REMARKS

Claims 6-11 constitute the pending claims in the present application. Claims 1-5 were previously cancelled. Claims 6-11 stand rejected. No claims are cancelled or amended herein.

1. Claim Rejections – 35 U.S.C. § 103 – Claims 6-11

Claims 6-11 are rejected under 35 U.S.C. § 103(a) as being allegedly obvious over the tri-combination of documents WO 03/049692 to Cioca et al. ("Cioca"), WO 97/016439 to Vigh et al. ("Vigh"), and WO 01/79174 to Urogdi et al. ("Urogdi"). Applicants respectfully traverse the rejection.

The cited combination of documents fails to render obvious the instant claims for at least the reason that, even taken together in view of the state of the art at the effective filing date of the present application, the documents would not have enabled the ordinary skilled worker to practice the claimed invention. Applicants generally refer the Office to their remarks presented in their November 11, 2011 Reply to non-Final Office Action ("Applicants' previous Reply"). Below, Applicants also address the Office's remarks on the present rejection from the outstanding Final Office Action.

In the outstanding Final Office Action, Applicants respectfully submit that, in order to support the outstanding obviousness rejection and to respond to Applicants' arguments on the impropriety of the rejection, the Office has made several errors mischaracterizing the cited art and relying on art not cited in the rejection.

Mischaracterization of the cited art. On page 5 of the outstanding Final Office Action, in addressing the predictability of the art, the Office contends that "the prior art recognized the ability of the increased expression of HSPs to treat neurodegeneration in the central nervous system, particular neurodegeneration related to ALS, as stated by Cioco et al (see also Kalmar et al and Bruening et al, previously made of record)." This is a mischaracterization of Cioco. The Cioco publication does not teach or suggest that "increased expression of HSPs [can] treat neurodegeneration in the central nervous system" as the Office suggests. Rather, the only relevant passage in Cioco states:

> It is, also, well established that stress proteins **are crucial** for the maintenance of cell health and integrity in some patho-physiological conditions that involve other tissues or organs, such as cardiomyopaties [sic], ischemia, amyotropic [sic] lateral sclerosis and Alzheimer's, Parkinson's and Huntington's diseases (J. Mol. Cell. Cardiol. 27, 45-52, 1995; J. Clin. Invest. 95, 1446-1456, 1995; Nature Medicine 3, 1150-1154, 1997, EP1020187 A).

See Cioco page 2, lines 19-24 (emphasis added). Hence, Cioco states only that stress proteins are "crucial," i.e., related in some unspecified, yet potentially important, way to "amyotropic [sic] lateral sclerosis and Alzheimer's, Parkinson's and Huntington's diseases." This passage does not teach or suggest whether HSP expression should be increased or decreased in order to treat the listed diseases. Nor does any other passage in Cioco or in any other art cited in the rejection. Hence, one of ordinary skill in the art would have had no ability to predict whether and the extent to which HSP expression would have to be agonized or antagonized in order to treat ALS and the other stated indications.

Of the three publications listed in the above passage from Cioco, the first two apply to cardiomyopathies, which are indications not recited by the pending claims. Similarly, the third publication relates to diabetic neuropathy, a peripheral nervous system indication, which, as discussed in Applicants' Reply dated February 10, 2009, is therefore also not recited by the pending claims. The final cited publication, EP1020187, discusses the effects on the mitochondrion after being subjected to heat shock and states only that the mitochondrion "may have a role in the aggravation by age of a number of neurodegenerative diseases (such as Parkinson's disease, Huntington's disease, Alzheimer's disease)" (*see* EP1020187 at paragraph 0007 – emphasis added), i.e., that the mitochondrion has an indeterminate role, if any role at all. Importantly, heat shock proteins are not mentioned, let alone whether they can provide therapeutic benefit through their agonism or antagonism.

Therefore, Cioco does not teach or suggest whether HSP expression should be increased or decreased in order to treat the diseases at issue. Vigh and Urogdi fail to cure this deficiency.

Reliance on art not cited in the rejection is improper. In support of the contention that "the prior art recognized the ability of the increased expression of HSPs to treat

neurodegeneration in the central nervous system, particular neurodegeneration related to ALS," the Office, quoted above, also cites to "Kalmar et al and Bruening et al, previously made of record." While Applicants acknowledge that Kalmar and Bruening have been cited in the present application in previous rejections, these publications have not been cited in the instant rejection and reliance on their disclosures without a formal citation in a rejection is improper.

Similarly, on page 5 of the outstanding Final Office Action, the Office asserts that "bimoclomol and its analogs were known to induce the expression of HSPs and provided neuroprotective activity *in vivo* (Kalmar et al, abstract and p. 87, right column)" and that "the prior recognizes an *in vivo* mouse model of ALS and the ability of the increased expression of HSPs to provide neuroprotection in said model (Bruening et al, abstract)." Again, neither Kalmar nor Bruening has been cited in the outstanding rejection, and therefore they are not a part of the rejection, and reliance on their disclosures is improper.

Applicants appreciate the Office's cooperation in creating a clear prosecution record for potential future review in litigation or other proceedings. *See* MPEP 707.07(f) ("In order to provide a complete application file history and to enhance the clarity of the prosecution history record, an examiner must provide clear explanations of all actions taken by the examiner during prosecution of an application." Therefore, without an explicit indication from the Office, Applicants will not assume that any particular publication is the basis of a given rejection, regardless of whether such a publication is already of record for another reason. To the extent that this requires the Office to attempt to make a *prima facie* case of obviousness by combining five publications (i.e., Cioco, Vigh, Urogdi, Kalmar, and Bruening), Applicants respectfully submit that this further suggests that such an obviousness rejection would be improper, at least because it illustrates the numerous assumptions and creative leaps required of the ordinary skilled worker.

The art cited in the rejection does not satisfy the *Wands* test for enablement. As noted in Applicants' previous Reply, the art cited in the present obviousness rejection (Cioco, Vigh, and Urogdi) has not been shown to enable the skilled worker to make and use the presently claimed invention. While Applicants highlighted that there is unpredictability because of the

lack of disclosure in Cioco, Vigh, and Urogdi on the link between HSP and ALS and the other indications and the lack of any disease models or working examples, the Office responded by arguing that there is predictability because the art knew to increase HSP expression to treat ALS and other diseases and that the art taught an *in vivo* model of the disease. However, at least because the Office did not rely on the art cited in the rejection, the Office has not shown that Cioco, Vigh, or Urogdi teach or suggest increasing or decreasing HSP expression to treat the recited indications or an *in vivo* model of any disease, and therefore the Office's arguments in response to predictability are unsupported.

On pages 5-6 of the outstanding Final Office Action, the Office suggested that the present situation is different from that presented in Example L of Exhibit A from Applicants' previous Reply (a print-out from the USPTO website providing guidance to Examiners on evaluating enablement in chemical and biotechnical patent applications). However, Applicants submit that the current obviousness rejection is analogous to that in Exhibit A's "Example L: Alzheimer's Disease." Notably, in Example L, no examples of the claimed compounds' ability to treat Alzheimer's disease are presented by the application, only that the compounds are able to bind to a receptor that is somehow involved. In the present case, not only do Cioca, Vigh, and Urogdi not provide any examples of arimoclomol in a relevant disease model, there are no examples of this compound binding to anything, and there is certainly no teaching or suggestion of activation or deactivation of HSP expression by arimoclomol, or even whether activation or deactivation is the desired mechanism to produce a therapeutic effect. Hence, the present scenario is an even stronger case of non-enablement than the Office's own Example L.

Lastly, in response to Applicants' arguments on the total lack of working examples presented by Cioca, Vigh, and Urogdi, on page 5 of the outstanding Final Office Action, the Office states that "the lack of working examples should never be the sole reasons for a determination of lack of enablement…" While Applicants do not disagree with this statement, the statement is inapposite to the current situation. The lack of working examples in the combination of Cioca, Vigh, and Urogdi is not the "sole" reason for the propriety of finding that

the ordinary skilled worker would not have been enabled to practice the claimed invention in light of these three publications.

As Applicants described at length in Applicants' previous Reply, most of the Wands Factors support a lack of enablement. For example, **the state of the prior art** supports lack of enablement because the art was underdeveloped: very little was known about the causes of neurodegenerative diseases, such as ALS, and there were no FDA-approved treatments. Furthermore, regarding **predictability or unpredictability of the art**, Applicants noted that there was little, if any, predictability, in particular because none of the cited art demonstrates any sort of relationship between arimoclomol and HSP, how HSP is implicated in any of the diseases (e.g., agonizes or antagonizes), or if HSP modulation would occur *in vivo* (e.g., no disease model). As for the **amount of direction or guidance presented**, Applicants discussed how Cioca, Vigh, and Urogdi provide little if any guidance because none of these publications teach or suggest how arimoclomol is to be used in an *in vitro* model of the stated diseases, let alone an *in vivo* model. Lastly, for the **quantity of experimentation necessary**, Applicants noted that the amount of experimentation would be enormous and undue because of Cioca, Vigh, and Urogdi's lack of disease models and lack of teaching or suggestion about the relationship between HSP and the diseases. Accordingly, the lack of working examples is not the "sole" reason for the lack of enablement because the other Wands Factors also support a finding of non-enablement.

The Office also states on page 5 of the outstanding Final Office Action that "the state of the prior art is related to the need for working examples in the specification." Applicants wholly agree and submitted in Applicants' previous Reply that the state of the prior art was very underdeveloped, which demonstrates the need for working examples to establish enablement. The Office has cited this statement and either not applied it in the present case or implied that the state of the art in treating ALS and other complex neurological diseases almost eight years ago was so advanced that working examples were unnecessary. Applicants respectfully submit that this was not the state of the prior art at the time of filing the present application.

In summary, for the numerous reasons above, the Cioca, Vigh, and Urogdi fail to enable one of ordinary skill to practice the claimed invention, and the outstanding obviousness rejection over these publications is therefore improper.

Lack of reasonable expectation of success. In addition to Cioca, Vigh, and Urogdi's inability to enable the ordinary skilled worker to practice the claimed invention, taken alone or in combination, these publications also would not have provided such a person with a reasonable expectation of success in arriving at the claimed invention by combining their teachings. In particular, these publications do not teach or suggest how to use arimoclomol for treatment of ALS and the other recited indications because without an *in vitro* or *in vivo* disease model they provide insufficient guidance.

Pursuant to MPEP 2143.02, "[t]he prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success" (citing *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986); emphasis added). Because there is not a reasonable expectation of success in combining the teachings of Cioca, Vigh, and Urogdi to arrive at the claimed invention, a *prima facie* obviousness rejection has not been established for this additional reason.

CONCLUSION

In view of the above remarks and amendments, Applicants submit that the pending application is in condition for allowance. The Examiner may address any questions raised by this submission to the undersigned at (212) 596-9000.

Applicants believe no fee other than that required for the above-mentioned extension o f time is due with this response. However, if an additional fee is due, please charge our Deposit Account No. 06-1075, under Order No. 109225-0018-101 from which the undersigned is authorized to draw.

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Respectfully submitted,

By_____

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